

**Supplementary figures and tables of the manuscript titled:**

**The prognostic value of the tumor-stroma ratio is most discriminative in patients with grade III or triple negative breast cancer.**

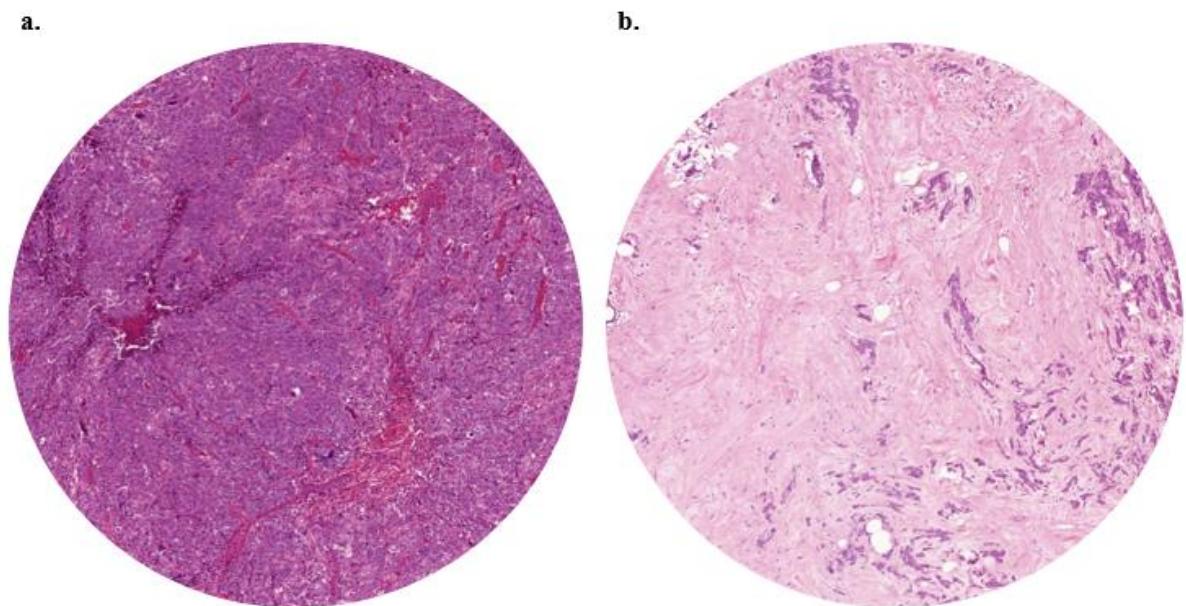
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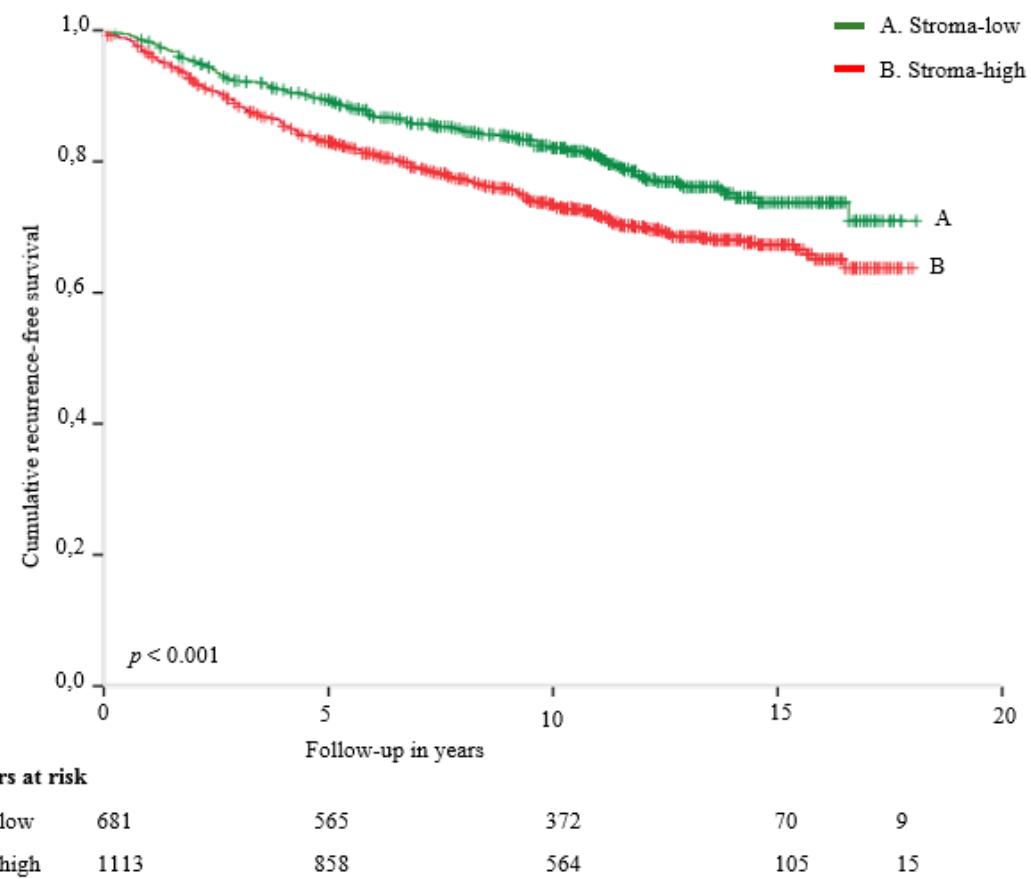
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**Supplementary figure 1.** Representative tissue selection for tumor-stroma ratio assessment.

**a.** Stroma-low, **b.** Stroma-high.



**Supplementary figure 2.** Kaplan-Meier analysis for recurrence-free survival of patients included in the Nottingham Breast Cancer Series stratified by tumor-stroma ratio.



**Supplementary table 1.** Overview of the stratification of age, tumor characteristics and treatment options of patients included in the ONCOPOOL study.

		<b>Stroma-low</b>		<b>Stroma-high</b>		
	n	n = 454	%	n = 283	%	p-value
<i>Age (in years)</i>						
<40	63	49	10.8	14	4.9	0.012
40-49	206	134	29.5	72	25.4	
50-59	259	147	32.4	112	39.6	
≥60	209	124	27.3	85	30.0	
<i>Histological type</i>						
Invasive carcinoma of NST	621	386	85.0	235	83.0	0.484
Lobular carcinoma	69	38	8.4	31	11.0	
Tubular carcinoma	32	22	4.8	10	3.5	
Others	15	8	1.8	7	2.5	
<i>Grade</i>						
I	159	101	22.2	58	20.5	0.274
II	255	146	32.2	109	38.5	
III	216	142	31.3	74	26.1	
Missing	107	65	14.3	42	14.8	
<i>Tumor size (in cm's)</i>						
≤2	479	314	69.2	165	58.3	0.005
>2-≤5	252	135	29.7	117	41.3	
>5	6	5	1.1	1	0.4	
<i>Nodal status</i>						
Negative	416	257	56.6	159	56.2	0.145
Positive	315	191	42.1	124	43.8	
Missing	6	6	1.3	0	0	
<i>ER status</i>						
Negative	127	87	19.2	40	14.1	0.142
Positive	606	365	80.4	241	85.2	
Missing	4	2	0.4	2	0.7	
<i>PR status</i>						
Negative	234	149	32.8	85	30.0	0.442
Positive	496	302	66.5	194	68.6	
Missing	7	3	0.7	4	1.4	
<i>HER2 status</i>						
Negative	573	357	78.6	216	76.3	0.462
Positive	151	91	20.0	60	21.2	
Missing	13	6	1.3	7	2.5	
<i>Chemotherapy</i>						
No	573	346	76.2	227	80.2	0.204
Yes	164	108	23.8	56	19.8	
<i>Hormonal therapy</i>						
No	369	229	50.4	140	49.5	0.798

Yes	368	225	49.6	143	50.5	
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Abbreviations: ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, NST = no special type, PR = progesterone receptor

**Supplementary table 2.** Univariate and multivariate Cox regression analysis of the ONCOPool study. The tumor-stroma ratio is adjusted for confounders.

		Recurrence-free survival						Overall survival					
		Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
		n	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI
<i>Age</i>													
	733	1.00	0.98 to 1.01	0.482	1.00	0.98 to 1.02	0.978	1.04	1.03 to 1.05	<0.001	1.04	1.03 to 1.06	<0.001
<i>Tumor size (in cm's)</i>													
≤2	479			<0.001			0.098			<0.001			0.028
>2	258	1.77	1.35 to 2.32		1.31	0.95 to 1.79		1.65	1.30 to 2.09		1.37	1.04 to 1.82	
<i>Grade</i>													
I	159			<0.001			0.022			<0.001			0.001
II	255	1.86	1.22 to 2.86		1.63	1.04 to 2.56		1.64	1.13 to 2.38		1.65	1.10 to 2.46	
III	216	2.51	1.64 to 3.85		2.00	1.22 to 3.28		2.47	1.71 to 3.56		2.24	1.46 to 3.43	
<i>Histological type</i>													
Invasive carcinoma of NST	621			0.657			0.464			0.461			0.326
Lobular carcinoma	69	0.99	0.63 to 1.56		1.32	0.74 to 2.35		0.93	0.62 to 1.40		1.11	0.63 to 1.97	
Tubular carcinoma	32	0.69	0.32 to 1.47		0.92	0.39 to 2.15		0.93	0.53 to 1.63		1.02	0.52 to 2.00	
Others	14	0.61	0.19 to 1.91		0.41	0.10 to 1.67		0.40	0.13 to 1.26		0.16	0.02 to 1.15	
<i>ER status</i>													
Negative	127			<0.001			0.542			<0.001			0.470
Positive	606	0.55	0.40 to 0.76		0.87	0.55 to 1.37		0.54	0.41 to 1.71		0.87	0.59 to 1.27	
<i>PR status</i>													
Negative	234			<0.001			0.271			<0.001			0.016
Positive	496	0.60	0.45 to 0.79		0.81	0.55 to 1.18		0.51	0.40 to 0.64		0.67	0.49 to 0.93	
<i>HER2 status</i>													
Negative	573			0.572			0.896			0.017			0.033
Positive	151	1.10	0.79 to 1.53		1.02	0.72 to 1.47		1.40	1.06 to 1.84		1.39	1.03 to 1.88	

<i>TSR</i>												
Stroma-low	454			0.093			0.085			0.016		0.029
Stroma-high	283	1.26	0.96 to 1.66		1.30	0.96 to 1.76		1.34	1.06 to 1.69		1.35	1.03 to 1.77

Abbreviations: ER = estrogen receptor, HER2= human epidermal growth factor receptor 2, NST = no special type, PR = progesterone receptor, TSR= tumor-stroma ratio

**Supplementary table 3.** Results of the independent prognostic value of the tumor-stroma ratio adjusted for confounders, triple-negative status and lymph node status calculated with multivariate Cox regression analysis in the ONCOPOOL study.

	<b>Recurrence-free survival</b>	<b>Overall survival</b>
Confounding factors	HR 1.30, 95% CI 0.96 to 1.76, $p = 0.085$	HR 1.35, 95% CI 1.03 to 1.77, $p = 0.029$
Confounding factors including triple-negative status	HR 1.30, 95% CI 0.96 to 1.75, $p = 0.091$	HR 1.34, 95% CI 1.02 to 1.74, $p = 0.033$
Confounding factors and lymph node status	HR 1.28, 95% CI 0.95 to 1.73, $p = 0.112$	HR 1.33, 95% CI 1.02 to 1.74, $p = 0.037$

**Supplementary table 4.** Results of tumor-stroma ratio stratified by clinically important prognostic parameters in the ONCOPOOL study and the multivariate Cox regression analysis per clinically relevant subgroup with a statistically significant difference in the Nottingham Breast Cancer series.

TSR stratified by group	Subgroups	Recurrence-free survival	Overall survival
<i>Age</i>		$p = 0.496$	$p = 0.840$
<i>Tumor size</i>		$p = 0.816$	$p = 0.823$
<i>Grade</i>		$p = 0.122$	$p = 0.414$
	Grade I	HR 0.92, 95% CI 0.39 to 2.35, $p = 0.992$	HR 0.83, 95% CI 0.38 to 1.81, $p = 0.631$
	Grade II	HR 1.06, 95% CI 0.66 to 1.70, $p = 0.806$	HR 1.30, 95% CI 0.83 to 2.02, $p = 0.257$
	Grade III	HR 1.86, 95% CI 1.18 to 2.93, $p = 0.008$	HR 1.61, 95% CI 1.08 to 2.41, $p = 0.020$
<i>Histological type</i>		$p = 0.838$	$p = 0.620$
<i>ER status</i>		$p = 0.445$	$p = 0.222$
<i>PR status</i>		$p = 0.982$	$p = 0.387$
<i>HER2 status</i>		$p = 0.646$	$p = 0.910$
<i>Triple-negative status</i>		$p = 0.343$	$p = 0.255$
	Non-triple-negative status	HR 1.25, 95% CI 0.91 to 1.73, $p = 0.176$	HR 1.28, 95% CI 0.96 to 1.72, $p = 0.093$
	Triple-negative status	HR 1.54, 95% CI 0.64 to 3.66, $p = 0.333$	HR 1.75, 95% CI 0.83 to 3.66, $p = 0.140$
<i>Lymph node status</i>		$p = 0.423$	$p = 0.097$

Abbreviations: ER = estrogen receptor, HER2 = human epidermal growth factor receptor, PR = progesterone receptor